This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1. (Currently amended) ~~A~~ An artificial membrane scaffold protein that will, in an aqueous environment, self assemble in the absence of phospholipid or with a phospholipid ~~ora~~ or a mixture of phospholipids, into a nanoscale particle between about 5 nm and about 500 nm in diameter, wherein said membrane scaffold protein is amphipathic, and wherein said membrane scaffold protein forms at least one alpha helix.

2. (Currently amended) The artificial membrane scaffold protein of claim 1, wherein said membrane scaffold protein assembles with a phospholipid or a mixture of phospholipids into a nanoscale particle of about 5 nm and about 500 nm in diameter, wherein a phospholipid bilayer is formed.

3. (Currently amended) The artificial membrane scaffold protein of claim 2, wherein the phospholipid bilayer is discoidal.

4. (Currently amended) The artificial membrane scaffold protein of claim 1, wherein said membrane scaffold protein ~~selfassembles~~ self assembles together with at least one hydrophobic or partially hydrophobic protein to form a nanoscale particle between about 5 nm and 500 nm in diameter, said nanoscale particles comprising the membrane scaffold protein and the at least one hydrophobic or partially hydrophobic protein.

5. (Currently amended) The artificial membrane scaffold protein of claim 1, wherein said membrane scaffold protein self assembles in the absence of phospholipid to form a nanoscale particle between about 5 nm and about 500 nm in diameter.

6. (Currently amended) The artificial membrane scaffold protein of claim 5, wherein said nanoscale particle is from about 5 to about 100 nm in diameter.

7. (Currently amended) The artificial membrane scaffold protein of claim 6, wherein said nanoscale particle is from about 5 to about 50 nm in diameter.

8. (Currently amended) The artificial membrane scaffold protein of claim 1, wherein said membrane scaffold protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:23, SEQ ID NO:29, SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45.

9. (Currently amended) A nanoscale particle comprising the artificial membrane scaffold protein of claim 1 and at least one hydrophobic or partially hydrophobic protein, and optionally further comprising a phospholipid or a mixture of phospholipids, wherein said nanoscale particle has a diameter between about 5 nm and about 500 nm.

10. (Original) The nanoscale particle of claim 9, wherein the hydrophobic or partially hydrophobic protein is a membrane protein.

11. (Withdrawn) The nanoscale particle of claim 10, wherein said membrane protein is a tethered membrane protein.

12. (Withdrawn) The nanoscale particle of claim 10, wherein the membrane protein is an embedded membrane protein.

13. (Original) The nanoparticle assembly of claim 10, wherein the membrane protein is an integral membrane protein.

14. (Original) The nanoscale particle of claim 13, wherein the membrane protein has seven transmembrane segments.

15. (Original) The nanoscale particle of claim 10, wherein said membrane protein is a receptor protein.

16. (Original) The nanoscale particle of claim 10, wherein said membrane protein is a G-protein coupled receptor.

17. (Original) The nanoscale particle of claim 16, wherein said G-protein coupled receptor is a 5-hydroxytryptamine receptor.

18. (Original) The nanoscale particle of claim 8, wherein said membrane scaffold protein is fused genetically with the hydrophobic protein.

19. (Currently amended) The nanoscale particle of claim 9, wherein said artificial membrane scaffold protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:23, SEQ ID NO:29, SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45.

20. (Withdrawn; currently amended) A method for incorporating at least one hydrophobic or partially hydrophobic protein into a nanoscale particle which is stable and soluble in aqueous solutions, said method comprising the step of allowing ~~a~~ an artificial membrane scaffold protein and at least one hydrophobic or partially hydrophobic protein to self assemble into nanoscale particles in an aqueous solution, optionally in the presence of at least one phospholipid, whereby nanoscale particles are formed.

21. (Withdrawn) The method of claim 20, wherein said at least one hydrophobic or partially hydrophobic protein is a membrane protein.

22. (Withdrawn) The method of claim 21, wherein said membrane protein is a tethered membrane protein, an embedded membrane protein or an integral membrane protein.

23. (Withdrawn) The method of claim 22, wherein said membrane protein is tissue factor.

24. (Withdrawn) The method of claim 21, wherein said membrane protein is a receptor protein.

25. (Withdrawn) The method of claim 24, wherein said receptor protein is a G-protein coupled receptor.

26. (Withdrawn) The method of claim 25, wherein said G-protein coupled receptor is a 5-hydroxytryptamine receptor.

27. (Withdrawn; currently amended) The method of claim 20, wherein said artificial membrane scaffold protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:23, SEQ ID NO:29, SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45.

28. (Withdrawn) The method of claim 20, wherein said at least one hydrophobic or partially hydrophobic protein is associated with membranes or membrane fragments.

29-33. (Canceled)

34. (Withdrawn; currently amended) A DNA molecule encoding ~~a~~ an artificial membrane scaffold protein, wherein said membrane scaffold protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:23, SEQ ID NO:29, SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45.

35. (Withdrawn) A recombinant host cell comprising the DNA molecule of claim 34.

36. (Withdrawn; currently amended) A method of using the DNA molecule of claim 34 to produce ~~a~~ an artificial membrane scaffold protein, said method comprising the steps of:

a) transforming a host cell capable of expressing ~~a~~ an artificial membrane scaffold protein, wherein the DNA molecule comprises a promoter functional in said host cell and a portion encoding the artificial membrane scaffold protein, said portion encoding the artificial membrane scaffold protein operably linked to the promoter; and

b) culturing the transformed host cell under conditions suitable for expression of said artificial membrane scaffold protein coding sequence, whereby the artificial membrane scaffold protein is produced.

REMARKS

Claims 1-10 and 13-19 have been examined.

Claim 1 and others have been amended to recite "artificial" membrane scaffold protein in accordance with the suggestion of the Examiner. This amendment is supported by the as-filed Specification at page 13, line 16, for example. Claims 1 and 4 have been amended to correct obvious inadvertent typographical errors. Claims 11-12, 20-28 and 34-36 have been withdrawn from consideration. Claims 29-33 have been canceled without prejudice. None of the amendments made herein constitutes the addition of new matter.

The Requirement for Restriction

The Patent Office has required restriction under 35 U.S.C. 121, alleging that the claims as filed embody four separately patentable inventions, as set forth below.

I. Claims 1-19, drawn to a membrane scaffold protein and a nanoscale particle comprising the membrane scaffold protein, classified in Class 530, subclass 350.

II. Claims 20-28, drawn to a method for incorporating at least one hydrophobic or partially hydrophobic protein into a nanoscale particle, classified in Class 435, subclass 7.1.

III. Claims 29-33, drawn to a method for identifying a competitor of binding of a ligand to a receptor protein wherein sad receptor protein in incorporated within a nanoscale particle, classified in Class 435, subclasses 7.1.

IV. Claims 34-35, drawn to a DNA molecule and host cells, classified in Class 536, subclass 23.5, 435, subclass 325.

Applicants provisionally elect with traverse the claims of Group I for examination. Applicants respectfully request the rejoinder of the claims of Group IV, claims 34-35, drawn to a DNA molecule and host cells. Claims 29-33 have been canceled without prejudice. In response to the requirement for the election of a particular species for examination, Applicants elect the species of membrane scaffold protein which is identified by SEQ ID NO:17 (MSP2, with histidine tag).

In traverse of the requirement for restriction between the claims of Group I and IV, Applicants urge that neither the membrane scaffold protein nor the DNA molecules encoding it are found in nature. There is no other purpose for the claimed DNA molecules other than for expression of the membrane scaffold proteins. A search of the protein, at least in the scientific literature, should be expected to uncover any references to the encoding DNA molecules.

With respect to the requirement to elect a particular species of membrane protein, tethered, embedded or integral, Applicants elect the integral membrane protein with traverse, and argue for examination of particles comprising all particular hydrophobic proteins. Traverse is made in view of the common way in which the membrane scaffold protein acts to support the hydrophobic protein in a nanoscale particle.

In traversal of the requirement for election of a particular sequence, Applicants note that the sequences are species within the genus of membrane scaffold protein; the unifying features of the membrane scaffold proteins of the present invention are taught at page 6, lines 10-19, and at page 13, line 16 through page 14, line 24. Applicants request the simultaneous examination of SEQ ID NOs:6 and 9. SEQ ID NO:9 is closely related to SEQ ID NO:6 in that NO:9 lacks the His tag sequence (twelve amino acids) at the N-terminus. MSP2 (SEQ ID NO:17) is related to SEQ ID NO:6 in that MSP2 contains the sequence of MSP1 (SEQ ID NO:6), followed by a Gly-Thr linker, followed by SEQ ID NO:9. The close structural relationship of all the specifically exemplified MSPs is shown in the following table. H1, H2, etc. are helix-forming domains within the MSPs and the table illustrates the modular structures of these MSPs.

Table 1.

Comparison of Modular Composition of Membrane Scaffold Proteins

MSP1	HisTag-H1-H2-H3-H4-H5-H6-H7-H8-H9-H10	(SEQ ID NO:6)
MSP1	------H1-H2-H3-H4-H5-H6-H7-H8-H9-H10	(SEQ ID NO:9)
MSP2	HisTag-H1-H2-H3-H4-H5-H6-H7-H8-H9-H10-gly-thr-H1-H2-H3-H4-H5-H6-H7-H8-H9-H10	(SEQ ID NO:17)
MSP1Δ3	HisTag-H1-H2----H4-H5-H6-H7-H8-H9-H10	(SEQ ID NO:43)
MSP1Δ2	HisTag-H1-H2-H3-H4-H5-H6-H7-H8----H10	(SEQ ID NO:44)
MSP1Δ4-5	HisTag-H1-H2-H3-H4-------H7-H8-H9-H10	(SEQ ID NO:23)

Applicants respectfully note that the membrane scaffold proteins of the present invention are artificial proteins, i.e., they do not occur in nature. See the definition of membrane scaffold protein in the as-filed Specification, at page 13, line 16, for example. The DNA molecules and host cells are also not natural products. Accordingly, it is urged that the claims to the proteins, DNA and host cells be simultaneously examined. In addition, Applicants again request consideration of claim 36, which is a linking claim; it is drawn to the method of producing an artificial membrane scaffold protein of the present invention using the DNA molecule which encodes it.

In view of the related technical and structural features of the membrane scaffold proteins, Applicants respectfully request the simultaneous examination of all the species of the membrane scaffold proteins of the present invention, the DNA molecules encoding them, recombinant host cells and methods of producing the membrane scaffold proteins using the DNA molecules/recombinant host cells of the present invention.

The Rejection under 35 U.S.C. 101

Claims 1-7 and 9 have been rejected under 35 U.S.C. 101 because the claimed invention is allegedly directed to nonstatutory subject matter, a membrane scaffold protein and a nanoscale particle comprising the membrane scaffold protein. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the claims read on products of nature, e.g., apo A-I and high density lipoprotein particles.

Applicants respectfully note that the present Specification defines the membrane scaffold proteins of the present invention as those which do **not** occur in nature. In the interest of advancing prosecution, Applicants have amended claim 1 to recite an **artificial** membrane scaffold protein. This amendment is supported by the as-filed Specification at page 6, line 10, and at page 13, line 16, for example. Because of the definition in the as-filed Specification, Applicants

respectfully maintain that the claims never read on nor were they intended to read on a product of nature.

In view of the definition in the Specification and the amendment to the claims, Applicants respectfully request the withdrawal of this rejection.

The Rejection under 35 U.S.C. 102

Claims 1-7, 9, 10 and 13 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Bayburt et al. (1998). Applicants respectfully traverse this rejection.

The Patent Office has stated that the Bayburt et al. reference teaches the reconstitution and imaging of an integral membrane protein in a nanometer size phospholipid bilayer structure consisting of a circular (discoidal) phospholipid domain stabilized by apoliprotein A1, an amphipathic membrane scaffold protein.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 1 to recite "artificial" membrane scaffold protein. Artificial membrane scaffold proteins of the present invention are distinct from apoliprotein AI in their amino acid sequences. This amendment is supported by Applicants' definition of membrane scaffold protein; see, e.g., page 13, line 16, and page 6, line 10.

In view of the amendment and the definition in the as-filed Specification, Applicants respectfully submit that the invention as claimed is not anticipated by the cited Bayburt et al. (1998) reference, and the withdrawal of the rejection is requested.

Claim Objections

Claims 1 and 4 have been objected to because of typographical errors. These inadvertent errors have been corrected in the present amendment.

Claims 8, 18 and 19 have been objected to because they recite unelected subject matter (amino acid sequences of SEQ ID NOs: 6, 9, 19, 23, 29, 43-45). Applicants have traversed the restriction above and continue below.

Applicants respectfully note that the MPEP at Section 803.04 indicates that up to 10 nucleotide sequences can be searched. It seems appropriate that there should be no greater burden to search up to 10 artificial protein sequences identified by their amino acid sequences. The Examiner did not cite any art which allegedly anticipates or renders obvious SEQ ID NO:17. Thus, Applicants respectfully request that the Patent Office search the remaining membrane scaffold protein sequences, i.e., SEQ ID NO:6, SEQ ID NO: 9, SEQ ID NO:19, SEQ ID NO:23, SEQ ID NO:29, SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45. The relationships of these sequences are shown in the table shown herein above.

Claims 14-17 have been objected to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claims and any intervening claims.

Applicants respectfully submit that with the amendment of claim 1, from which claims 14-17 ultimately depend, to recite an artificial membrane scaffold protein, claims 14-17 should be found allowable in their present form. Applicants further request consideration of claims reciting other types of membrane proteins incorporated in the Nanodiscs.

The Information Disclosure Statement

Applicants had provided an Information Disclosure Statement in compliance with 37 C.F.R. 1.56 and 1.97-1.98, including a Form PTO-1449 and photocopies of 42 references. A copy of the Return Receipt Postcard stamped by the Patent and Trademark Office on March 27, 2002 is submitted herewith, together with a complete copy of the submission which complete copy is identical to that filed by Express Mail on March 27, 2002. This is in response to the Examiner's request in the telephone interview of July 1, 2003.

Applicants respectfully request that the Examiner consider the references cited on the PTO Form 1449 and provide an initialed copy with the next action.

The Telephone Interview

Applicants appreciate the Examiner's assistance in the telephone interview of July 1, 2003. In particular, the Examiner indicated that the one month period noted on the Office Action for response was incorrect and that response within three months of the June 11, 2003 mailing date would not require a Petition for Extension of Time or fee.

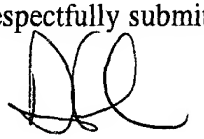
Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

It is believed that the present Amendment does not necessitate the payment of any fees under 37 C.F.R. 1.16-1.17. If this is incorrect, please deduct any fee due under the foregoing Rules to Deposit Account No. 07-1969, and consider the present submission to include a Petition for Extension of Time.

Respectfully submitted,



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